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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,217	11/18/2005	Masaomi Tajimi	RCK-40	2662

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Barbara A. Shimei
Director, Patents & Licensing
Bayer HealthCare LLC - Pharmaceuticals
555 White Plains Road, Third Floor
Tarrytown, NY 10591

EXAMINER	
O DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,217	TAJIMI ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,20,23 and 25-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,20,23 and 25-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-5, 7, 20, 23, 25-28 are pending in the current application.

2. This is application is a national stage of PCT/EP2003/013452, filed November 28, 2003, which claims the priority of European Union Application EP 02027528.5, filed December 9, 2002.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 30, 2008 has been entered.

Response to Arguments

3. Applicant's arguments filed April 20, 2008 have been fully considered but they are not fully persuasive. The enablement rejection for the compounds is withdrawn. With respect to the rejection under and 112 1st paragraph for enablement for the treatment of pain the rejection is maintained. It should be clear that the assays of the specification, save the cell based capsaicin antagonism, are entirely prophetic. The examiner indicated that treatment of pain was a valid goal of TRPV1 antagonist development, which is what these references cited by the applicant testify to and were not ignored. The examiner has introduced a substantial body of evidence to indicate that the claims are not enabled. Again as the examiner pointed out previously capsaicin is not the endogenous ligand for TRPV1, and the ligand is currently unknown (see the previous discussion). It is very clear that the cell based assays do not correlate with treatment, and in

general neither do animal assays. It is clear that rabbits cannot be treated because they do not respond to capsaicin. How can rabbits be treated with these compounds? In the instant case, given the total lack of predictability and the paucity of data provided a lack of enablement was entirely appropriate and is maintained. The remaining double patenting rejections are maintained for the reasons of record, since the '848 and '27 applications have common inventors regardless of the assignment. The terminal disclaimer was not approved because the attorney or agent is not of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite where the compound "is a VR1 antagonist".

> 7. (Previously Presented) The pharmaceutical composition as claimed in claim 5, wherein said tetrahydro-naphthalene derivative of the formula (I), its tautomeric or stereoisomeric form, or a physiologically acceptable salt thereof is a VR1 antagonist.

Functional language as that of the instant claims carries no patentable weight in claims for compositions of matter see *Union Oil Co. of California v. Atlantic Richfield Co.* 54 USPQ2d 1227 where "composition claims cannot, as the appellant refiners argue, embrace only certain uses of that composition. (citing In Re Spada) Otherwise these composition claims would mutate

into method claims." It is recommended that this claim be canceled or rewritten with the removal of the intended use recitation.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 20, 23, 25-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for a handful of compounds that might be useful in treating pain in rodents, it does not reasonably provide enablement for the excessively protracted list of compounds and diseases claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The pharmacology of TRPV1 is complex, with the receptor expressed both centrally and peripherally. It is worth pointing out that while capsaicin is an effective tool as agonist when

doing high-throughput pharmacology, it is not the endogenous ligand for TRPV1. Protons and heat and possibly a few lipids are thus far the only known endogenous ligands for this receptor. Is this antagonism competitive or non-competitive? We do not know. While these compounds are reported to have "strong activity" the language employed in the specification (not past tense) suggests that these experiments were either being performed or were not performed at the time of filing. Regardless for pain treatment we have only rat DRG cell data to rely upon and as pointed out by Szallasi et. al. *TRENDS in Molecular Medicine* **2006**, *12*, 545-554:

> "Given the species-related differences in both the neurochemistry of capsaicin-sensitive neurons [2] and the pharmacological properties of TRPV1 [99], one should exercise utmost caution when extrapolating results obtained in rodents to humans."

So while potentially useful for treating pain in some rodents, we cannot believe that these compounds would be useful for treating pain in humans. The species variation of the receptor in mammals is quite significant as has been summarized by Ohta et. al. *Biochemical Pharmacology* **2005**, *71*, 173-187, pg. 174 column 1:

> "There are some notable species differences in the compound sensitivities of these channels. For instance, capsaicin has an agonistic action in most mammalian orthologues except for rabbit TRPV1 [12]. Indeed, rabbit dorsal root ganglion (DRG) neurons are resistant to the acute toxicity of capsaicin [18] and have no resiniferatoxin-binding site [19]. Furthermore, human [10] and guinea-pig TRPV1 [11] have little sensitivity to PPAHV, while rat [10,20], mouse [13] and dog TRPV1 [14] are significantly sensitive to PPAHV. RTX is more potent than olvanil in guinea-pig TRPV1 [11], but it is the opposite in other species [13–15,20]. Capsazepine, a TRPV1

> antagonist, inhibits the response to acidic pH in human [10] and guinea-pig TRPV1 [11], but not in rat [10] and mouse TRPV1 [13]. For studying pain research in vivo, a number of reports have been published using rodent models. However, because of the inability of capsazepine to inhibit all modes of rat and mouse TRPV1 activation, it is suggested that use of a rodent model for studying TRPV1 antagonists may not accurately reflect the role of TRPV1 in human pathophysiology [13]."

It is abundantly clear that rabbits will not benefit from a molecule that antagonizes the effects of capsaicin since they lack sensitivity to capsaicin. In addition, the animal models chosen will not accurately predict the use of these compounds in humans. The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a):

"A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make or use this very broad invention that has few working examples in this unpredictable art without undue experimentation.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re*

Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1-5, 7, 20, 23, 25-28 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-4, 8-20 of copending Application No. 10/513,848. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application and the referenced copending application would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: The Markush structures of the copending application have significant overlap with those of the instant case. The method claims from which they depend are essentially the same.

7. Claims 1-5, 7, 20, 23, 25-28 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-4, 6-22 of copending Application No. 10/575,027. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application and the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: The Markush structures of the copending application have significant overlap

with those of the instant case. The method claims from which they depend are essentially the same.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Thu 8:30 A.M.-7:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

/Rita J. Desai/
Primary Examiner, Art Unit 1625